PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MISHRA ET AL.

Application No. 09/820,371 Art Unit: 1617

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For: INJECTABLE AQUEOUS DISPERSIONS OF PROPOFOL

PENDING CLAIMS AFTER AMENDMENTS MADE IN RESPONSE TO OFFICE ACTION DATED OCTOBER 24, 2002

31. A method of reducing or substantially completely eliminating irritation around the site of injection upon injection of a formulation containing propofol comprising administering as a bolus intravenous injection or as an intravenous infusion at the injection site a stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1 % to about 15% of propofol, 1% up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and an aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier in a quantity sufficient to render the final composition isotonic with blood, wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents.

32. The method of claim 31, wherein the ratio of propofol to diluent is about 1:4 to about 1:0.1.

33. The method of claim 31, wherein the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.

34. The method of claim 31, wherein the dispersion has a viscosity of from about 1.5 to about 8 centipoise.

35. The method of claim 31, wherein the ratio of propofol to diluent is about 1:4 to about 1:0.1, and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the dispersion has a viscosity of from about 1.5 to about 8 centipoise.

36. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol, 1% up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and an aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier in a quantity sufficient to render the final composition isotonic with blood, wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents.

37. The method of claim 36, wherein the ratio of propofol to diluent is about 1:4 to about 1:0:1.

38. The method of claim 36, wherein the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.

39. The method of claim 36, wherein the dispersion has a viscosity of from about 1.5 to about 8 centipoise.

40. The method of claim 36, wherein the ratio of propofol to diluent is about 1:4 to about 1:0.1, and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the dispersion has a viscosity of from about 1.5 to about 8 centipoise.

41. The method of claim 31 or 36, wherein the propofol-soluble diluent is selected from the group consisting of isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, triglycerides of medium chain fatty acids, and combinations thereof.

42. The method of claim 31 or 36, wherein the propofol-soluble diluent is selected from the group consisting of pharmaceutically acceptable natural triglycerides from vegetable sources, pharmaceutically acceptable natural triglycerides from animal sources, pharmaceutically acceptable vegetable oils, omega-3 polyunsaturated fish oils, and combinations thereof.

43. The method of claim 31 or 36, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3- phosphocholine, 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], egg lecithin, egg phosphatidylcholine, soy phosphatidylcholine, saturated soy phosphatidylcholine, soy lecithin, dimyristoylphosphatidylcholine, dimyristoylphosphatidylglycerol, hydrogenated lecithin, and combinations thereof.

44. The method of claim 31 or 36, wherein the tonicity modifier is selected from the group consisting of sucrose, dextrose, trehalose, mannitol, lactose, glycerol, and combinations thereof.

45. The method of claim 31 or 36, wherein the dispersion is suitable for intravenous injection.

46. The method of claim 31 or 36, wherein propofol is present in an amount of about 2% by weight of the dispersion.

47. The method of claim 31 or 36, wherein the propofol-soluble diluent is a triglyceride of medium chain fatty acids.

48. The method of claim 31 or 36, wherein the polyhydroxy tonicity modifier is mannitol.

49. The method of claim 31 or 36, wherein the propofol concentration is about 2%, the propofol-soluble diluent is a triglyceride of medium chain fatty acids, the polyhydroxy tonicity modifier is mannitol, and the surface stabilizing amphiphilic agent is egg lecithin.

50. The method of claim 31 or 36, wherein propofol is present in an amount of about 2% to 5% by weight of the dispersion.

51. The method of claim 31 or 36, wherein the polyhydroxy additive is present in an amount of about 2.5% to about 20% by weight of the dispersion.

52. The method of claim 48, wherein mannitol is present in an amount of about 5.5% by weight of the dispersion.

53. The method of claim 31 or 36, wherein the propofol-soluble diluent is a mixture of medium-chain triglycerides.

54. The method of claim 53, wherein the triglyceride is a triglyceride of medium-chain fatty acids of synthetic or natural origin.

55. The method of claim 53, wherein the triglyceride is present in an amount of 2% to 6% by weight of the dispersion.

56. The method of claim 47, wherein the triglyceride is a triglyceride of medium-chain fatty acids of synthetic or natural origin.

57. The method of claim 47, wherein the triglyceride is present in an amount of 2% to 6% by weight of the dispersion.

58. The method of claim 47, wherein the triglyceride is present in an amount of 2% to 4% by weight of the dispersion.

59. The method of claim 58, wherein the triglyceride is present in an amount of 4% by weight of the dispersion.

60. The method of claim 53, wherein the mixture of medium-chain triglycerides is present in an amount of 4% by weight of the dispersion.

61. The method of claim 31 or 36, wherein the amphiphilic agent is egg lecithin.

62. The method of claim 61, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion.

63. The method of claim 62, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion.

64. The method of claim 31 or 36, which includes dimyristoylphosphatidyl glycerol.

65. The method of claim 64, wherein the dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

66. The method of claim 65, wherein the dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

67. The method of claim 36, which includes egg lecithin and dimyristoylphosphatidyl glycerol.

68. The method of claim 67, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion and the dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

69. The method of claim 68, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion and the dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

70. The method of claim 36, wherein the pH of the composition is about 4 to about 9.

71. The method of claim 36, wherein the pH of the composition is about 5 to about 8.

72. The method of claim 31 or 36, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

73. The method of claim 31 or 36, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

74. The method of claim 72, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

75. The method according to claim 31 or 36, wherein the dispersion is steam sterilizable.

76. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm, the dispersion consisting essentially of

(a) between about 1% to about 15% of propofol;

(b) between about 1% to about 8% of a propofol-soluble diluent;

(c) between about 0.5% to about 5% of a surface stabilizing amphiphilic agent; and

(d) a pharmaceutically acceptable water-soluble polyhydroxy additive that acts as a tonicity modifier; and

(e) water;

(f) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise,

wherein the dispersion

prevents microbial growth, defined as no more than 0.5 log increase from the initial inoculum, of each of *Staphylococcus aureus, Escherichia coli, Pseudomonas*

aeruginosa, Candida albicans, and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said dispersion at approximately 1000 colony forming units per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viability of the microorganisms in the inoculated dispersion as determined by counting the colonies of said organism after 24, 48 hours and 7 days; and

results in no irritation at the site of injection as evidenced by a test wherein said dispersion is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

77. The method of claim 76, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

78. The method of claim 76, wherein the propofol-soluble diluent is selected from the group consisting of a synthetic fatty acid triglyceride, a natural fatty acid triglyceride, and mixtures thereof.

79. The method of claim 76, wherein the ratio of propofol to the propofol-soluble diluent is from about 1:3 to about 1:0.5.

80. The method of claim 76, wherein the ratio of propofol to the propofol-soluble diluent is from about 1:2 to about 1:1.

81. The method of claim 76, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

82. The method of claim 81, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

83. The method of claim 76, wherein the composition contains about 2% to about 10% of propofol.

84. The method of claim 76, wherein the pharmaceutically acceptable water-soluble polyhydroxy additive provides the propofol-containing dispersion or composition with an osmolality of about 250 to about 700 milliosmolal.

85. The method of claim 84, wherein the osmolality is about 300 to about 500 milliosmolal.

86. The method of claim 76, wherein the viscosity is from about 2 to about 5 centipoise.

87. A method of causing no irritation at the site of injection upon injection of an injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm, the dispersion being capable of inhibiting the growth of microorganisms and consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, water, and a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents.

88. The method of claim 87, where the propofol and diluent are present in a ratio of about 1:4 to about 1:0.1 of propofol to diluent.

89. The method of claim 87, where the propofol and amphiphilic agent are present in a ratio of about 1:0.8 to about 1:2.5 of propofol to amphiphilic agent.

90. The method of claim 87 that has a viscosity of from about 0.8 to about 15 centipoise.

91. The method of claim 87, wherein the propofol-soluble diluent is selected from the group consisting of a pharmaceutically acceptable saturated fatty acid triglyceride, a pharmaceutically acceptable unsaturated fatty acid triglyceride, and mixtures thereof.

92. The method of claim 87, wherein the propofol-soluble diluent is selected from the group consisting of pharmaceutically acceptable esters of medium chain fatty acids, pharmaceutically acceptable esters of long chain fatty acids, pharmaceutically acceptable triglycerides of medium chain fatty acids, and mixtures thereof.

93. The method of claim 87, wherein the propofol-soluble diluent is selected from the group consisting of isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, and mixtures thereof.

94. The method of claim 87, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

95. The method of claim 94, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

96. The method of claim 87, which contains about 2% to about 10% of propofol.

97. The method of claim 87, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

98. The method of claim 87, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of charged phospholipid of natural sources, uncharged

phospholipid of natural sources, hydrogenated lecithin, a synthetic phospholipid, a poloxamer, a poloxamine, a polyoxyethylene sorbitan ester, and mixtures thereof.

99. The method of claim 87, wherein the surface stabilizing amphiphilic agent is a combination of cholesterol and one or more charged or uncharged phospholipid of natural sources, hydrogenated lecithin, or synthetic phospholipids.

100. The method of claim 87, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine, 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], egg lecithin, egg phosphatidylcholine, soy phosphatidylcholine, saturated soy phosphatidylcholine, soy lecithin, dimyristoylphosphatidylcholine, and dimyristoylphosphatidylglycerol.

101. The method of claim 87, wherein the dispersion elicits an anesthetic effect in a warm-blooded animal and human subject upon intravenous administration.

102. The method of claim 87, wherein the tonicity modifier is selected from the group consisting of sucrose, dextrose, trehalose, mannitol, lactose, glycerol, and mixtures thereof.

103. The method of claim 87, wherein the dispersion is isotonic with blood.

104. The method of claim 87, wherein the dispersion is suitable for intravenous injection.

105. The method of claim 87, wherein the dispersion contains a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier in an amount to provide an osmolality of about 250 to about 700 milliosmolal.

106. The method of claim 105, wherein the osmolality is about 300 to about 500 milliosmolal.

107. The method of claim 87, wherein the dispersion has a viscosity from about 2 to about 5 centipoise.

108. The method of claim 36, wherein inducing anesthesia comprises producing and maintaining at least one of ambulatory anesthesia, neurosurgical anesthesia, pediatric anesthesia, monitored anesthetic care, intensive care sedation, chronic sedation, general anesthesia, low dose sedation, and long-term sedation.

109. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount from about 1% to about 15% by weight of the dispersion;

(b) a propofol-soluble diluent in an amount from about 1% to about 8% by weight of the dispersion;

(c) a surface stabilizing amphiphilic agent in an amount from about 0.5% to about 5% by weight of the dispersion;

(d) a pharmaceutically acceptable water-soluble polyhydroxy additive; and

(e) water;

(e) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5 and the composition has a viscosity of about 0.8 to about 15 centipoise;

wherein the dispersion prevents microbial growth of no more than 0.5 log increase from the initial inoculum, of any one of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans,* and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of the microbe is added to an aliquot of said dispersion at approximately 1000 colony forming units per mL, at a temperature in the range of 20-25°C, whereafter said aliquot is incubated at 20-25°C and tested for

viability of the microbe in the inoculated dispersion as determined by counting the colonies of the microbe after 24 hours, 48 hours, and 7 days; and

wherein the dispersion results in no irritation at the site of injection as evidenced by a test wherein said dispersion is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

110. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount of about 2% by weight of the dispersion;

(b) a medium-chain triglyceride in an amount of 4% by weight of the dispersion;

(c) egg lecithin in an amount of 1.6% by weight of the dispersion;

(d) dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion;

(e) mannitol in an amount of 5.5% by weight of the dispersion; and

(f) water.

111. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount of about 2% by weight of the dispersion;

(b) a mixture of medium-chain triglycerides in an amount of 4% by weight of the dispersion;

(c) egg lecithin in an amount of 1.6% by weight of the dispersion;

(d) dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion;

(e) mannitol in an amount of 5.5% by weight of the dispersion; and

(f) water.

112. The method of claim 110, wherein the medium chain triglyceride is of synthetic or natural origin.

113. The method of claim 110, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

114. The method of claim 110, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

115. The method of claim 113, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

116. The method of claim 110, wherein the dispersion is steam sterilizable.

117. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of an injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm capable of inhibiting the growth of microorganisms, the dispersion consisting essentially of:

propofol in an amount of about 2% by weight of the dispersion;

a medium-chain triglyceride in an amount of 4% by weight of the dispersion;

egg lecithin in an amount of 1.6 % by weight of the dispersion;

dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion; and

mannitol in its aqueous phase in an amount of 5.5% by weight of the dispersion;

wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents and causes no irritation at the site of injection.

118. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthetic-inducing amount of an injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm capable of inhibiting the growth of microorganisms, the dispersion consisting essentially of:

propofol in an amount of about 2% by weight of the dispersion;

a mixture of medium-chain triglycerides in an amount of 4% by weight of the dispersion;

egg lecithin in an amount of 1.6 % by weight of the dispersion;

dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion; and

mannitol in its aqueous phase in an amount of 5.5% by weight of the dispersion; wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents and causes no irritation at the site of injection.

119. The method of claim 117, wherein the medium chain triglyceride is of synthetic or natural origin.

120. The method of claim 117, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

121. The method of claim 117, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

122. The method of claim 120, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

123. The method of claim 117, wherein the dispersion is steam sterilizable.